

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/18, 31/19, 31/44, 31/47, 31/195, 31/405, 31/415, 31/425, 31/435, 31/505, C07C 63/00, 307/06, 307/08, 307/10, C07D 209/40, 213/89, 217/08, 233/44, 233/88, 239/08, 239/14, 239/42	A1	(11) International Publication Number: WO 98/18461
		(43) International Publication Date: 7 May 1998 (07.05.98) <i>State</i>
(21) International Application Number: PCT/US97/19349 (22) International Filing Date: 27 October 1997 (27.10.97) (30) Priority Data: 60/029,223 30 October 1996 (30.10.96) US 9626308.2 18 December 1996 (18.12.96) GB (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DUGGAN, Mark, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HARTMAN, George, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HOFFMAN, William, F. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). IHLE, Nathan, C. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: INTEGRIN ANTAGONISTS		
(57) Abstract This invention relates to certain novel compounds and derivatives thereof, their synthesis, and their use as vitronectin receptor antagonists. The vitronectin receptor antagonist compounds of the present invention are $\alpha v\beta 3$ antagonists, $\alpha v\beta 5$ antagonists or dual $\alpha v\beta 3/\alpha v\beta 5$ antagonists useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation and tumor growth. <div style="text-align: center; font-size: 2em; margin-top: 100px;"><i>9/916, 977</i></div>		

WHAT IS CLAIMED IS:

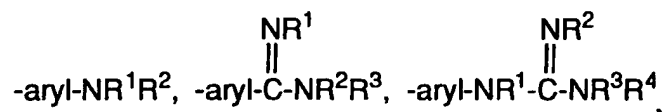
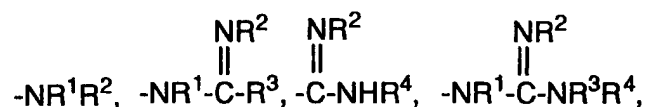
1. A compound of the formula

5 X-Y-Z-Ring-A-B

wherein:

10 Ring is a 4 to 10-membered mono-or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S, and either unsubstituted or substituted with R²⁷ and R²⁸;

X is selected from



15 or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R¹³, R¹⁴, R¹⁵ or R¹⁶;

20 Y is selected from

C₀₋₈ alkylene,

C₃₋₁₀ cycloalkyl,

C₀₋₈ alkylene-NR⁵-CO-C₀₋₈ alkylene,

C₀₋₈ alkylene-CONR⁵-C₀₋₈ alkylene,

25 C₀₋₈ alkylene-O-C₀₋₈ alkylene,

C₀₋₈ alkylene-NR⁵-C₀₋₈ alkylene,

C₀₋₈ alkylene-S(O)₀₋₂-C₀₋₈ alkylene,

C₀₋₈ alkylene-SO₂-NR⁵-C₀₋₈ alkylene,

C₀₋₈ alkylene-NR⁵-SO₂-C₀₋₈ alkylene,

30 C₀₋₈ alkylene-CO-C₀₋₈ alkylene,

$(\text{CH}_2)_{0-6} \text{ aryl} (\text{CH}_2)_{0-6}$,
 $(\text{CH}_2)_{0-6} \text{ aryl-CO-} (\text{CH}_2)_{0-6}$,
 $(\text{CH}_2)_{0-6} \text{ aryl-CO-NR}^5\text{-(CH}_2)_{0-6}$,
 $(\text{CH}_2)_{0-6} \text{ aryl-NR}^5\text{-CO-} (\text{CH}_2)_{0-6}$, or

$(\text{CH}_2)_{0-8} \text{CH}(\text{CH}_2)_{0-8}$;

Z is selected from

$(\text{CH}_2)_m$, $(\text{CH}_2)_m \text{O} (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{NR}^6 (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{NR}^6 \text{C}(=\text{O}) \text{NR}^7 (\text{CH}_2)_n$

$(\text{CH}_2)_m \text{C}(=\text{O}) \text{NR}^6 (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{NR}^6 \text{C}(=\text{O}) (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{C}(=\text{O}) (\text{CH}_2)_n$,

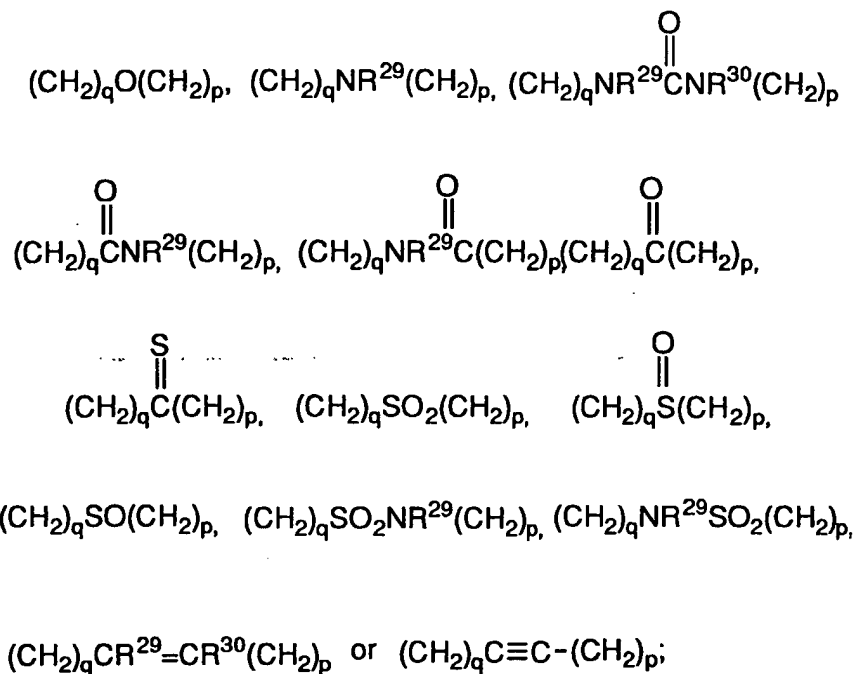
$(\text{CH}_2)_m \text{C}(=\text{S}) (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{SO}_2 (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{S}(=\text{O}) (\text{CH}_2)_n$,

$(\text{CH}_2)_m \text{SO} (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{SO}_2 \text{NR}^6 (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{NR}^6 \text{SO}_2 (\text{CH}_2)_n$,

$(\text{CH}_2)_m \text{CR}^6=\text{CR}^7 (\text{CH}_2)_n$, or $(\text{CH}_2)_m \text{C}\equiv\text{C}-(\text{CH}_2)_n$;

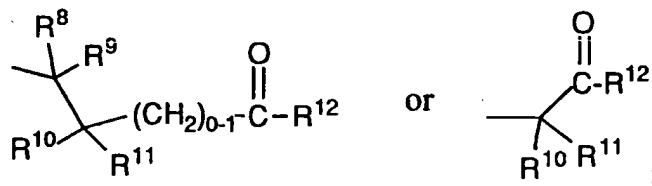
where m and n are each independently an integer from 0 to 6;

A is selected from



where p and q are each independently an integer from 0 to 6;

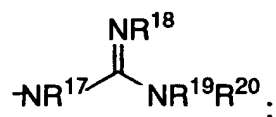
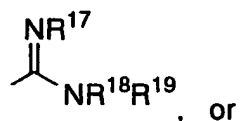
5 B is selected from



R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵,
 R²⁶, R²⁷, R²⁸, R²⁹ and R³⁰ are each independently selected from

- 10 hydrogen,
 halogen,
 C₁₋₁₀ alkyl,
 aryl C₀₋₈ alkyl,
 amino C₀₋₈ alkyl,
 15 C₁₋₃ acylamino C₀₋₈ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,

- C₁₋₆ dialkylamino C₀₋₈ alkyl,
 aryl C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₁₋₄ alkoxyamino C₀₋₈ alkyl,
 hydroxy C₁₋₆ alkylamino C₀₋₈ alkyl,
 5 C₁₋₄ alkoxy C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyloxy,
 hydroxy C₁₋₆ alkylamino C₀₋₆ alkyl,
 10 hydroxy C₀₋₆ alkyl,



- R⁸ and R⁹ are each independently selected from
 hydrogen,
 15 aryl,
 halogen,
 aryl-(CH₂)_p-,
 hydroxyl,
 C₁₋₈ alkylcarbonylamino,
 20 aryl C₁₋₅ alkoxy,
 C₁₋₅ alkoxycarbonyl,
 aminocarbonyl,
 C₁₋₈ alkylaminocarbonyl,
 C₁₋₆ alkylcarbonyloxy,
 25 C₃₋₈ cycloalkyl,
 amino,
 C₁₋₆ alkylamino,
 amino C₁₋₆ alkyl,
 arylaminocarbonyl,

- aryl C₁₋₅ alkylaminocarbonyl,
 aminocarbonyl,
 aminocarbonyl C₁₋₆ alkyl,
 hydroxycarbonyl,
 5 hydroxycarbonyl C₁₋₆ alkyl,
 C₁₋₈ alkyl, either unsubstituted or substituted, with one or more
 groups selected from: halogen, hydroxyl,
 C₁₋₅ alkylcarbonylamino, aryl C₁₋₅ alkoxy,
 C₁₋₅ alkoxycarbonyl, aminocarbonyl, C₁₋₅ alkylamino-
 10 carbonyl, C₁₋₅ alkylcarbonyloxy, C₃₋₈ cycloalkyl, oxo,
 amino, C₁₋₃ alkylamino, amino C₁₋₃ alkyl, arylamino-
 carbonyl, aryl C₁₋₅ alkylaminocarbonyl, aminocarbonyl,
 aminocarbonyl C₁₋₄ alkyl, hydroxycarbonyl, or
 hydroxycarbonyl C₁₋₅ alkyl,
 15 HC≡C(CH₂)_r -
 C₁₋₆ alkyl-C≡C(CH₂)_r -,
 C₃₋₇ cycloalkyl-C≡C(CH₂)_r -,
 aryl-C≡C(CH₂)_r -,
 C₁₋₆ alkylaryl-C≡C(CH₂)_r -,
 20 H₂C=CH(CH₂)_r -,
 C₁₋₆ alkyl-CH=CH(CH₂)_r -,
 C₃₋₇ cycloalkyl-CH=CH(CH₂)_r -,
 aryl-CH=CH(CH₂)_r -,
 C₁₋₆ alkylaryl-CH=CH(CH₂)_r -,
 25 C₁₋₆ alkyl-SO₂(CH₂)_r -,
 C₁₋₆ alkylaryl-SO₂(CH₂)_r -,
 C₁₋₆ alkoxy,
 aryl C₁₋₆ alkoxy,
 aryl C₁₋₆ alkyl,
 30 C₁₋₆ alkylamino C₁₋₆ alkyl,
 arylamino,
 arylamino C₁₋₆ alkyl,
 aryl C₁₋₆ alkylamino,
 aryl C₁₋₆ alkylamino C₁₋₆ alkyl,

arylcarbonyloxy,
aryl C₁₋₆ alkylcarbonyloxy,
C₁₋₆ dialkylamino,
C₁₋₆ dialkylamino C₁₋₆ alkyl,
5 C₁₋₆ alkylaminocarbonyloxy,
C₁₋₈ alkylsulfonylamino,
C₁₋₈ alkylsulfonylamino C₁₋₆ alkyl,
arylsulfonylamino C₁₋₆ alkyl,
aryl C₁₋₆ alkylsulfonylamino,
10 aryl C₁₋₆ alkylsulfonylamino C₁₋₆ alkyl,
C₁₋₈ alkoxy carbonylamino,
C₁₋₈ alkoxy carbonylamino C₁₋₈ alkyl,
aryloxy carbonylamino C₁₋₈ alkyl,
aryl C₁₋₈ alkoxy carbonylamino,
15 aryl C₁₋₈ alkoxy carbonylamino C₁₋₈ alkyl,
C₁₋₈ alkylcarbonylamino,
C₁₋₈ alkylcarbonylamino C₁₋₆ alkyl,
arylcarbonylamino C₁₋₆ alkyl,
aryl C₁₋₆ alkylcarbonylamino,
20 aryl C₁₋₆ alkylcarbonylamino C₁₋₆ alkyl,
aminocarbonylamino C₁₋₆ alkyl,
C₁₋₈ alkylaminocarbonylamino,
C₁₋₈ alkylaminocarbonylamino C₁₋₆ alkyl,
arylaminocarbonylamino C₁₋₆ alkyl,
25 aryl C₁₋₈ alkylaminocarbonylamino,
aryl C₁₋₈ alkylaminocarbonylamino C₁₋₆ alkyl,
aminosulfonylamino C₁₋₆ alkyl,
C₁₋₈ alkylaminosulfonylamino,
C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
30 arylaminosulfonylamino C₁₋₆ alkyl,
aryl C₁₋₈ alkylaminosulfonylamino,
aryl C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
C₁₋₆ alkylsulfonyl,
C₁₋₆ alkylsulfonyl C₁₋₆ alkyl,
35 arylsulfonyl C₁₋₆ alkyl,

- 5 aryl C₁₋₆ alkylsulfonyl,
aryl C₁₋₆ alkylsulfonyl C₁₋₆ alkyl,
C₁₋₆ alkylcarbonyl,
C₁₋₆ alkylcarbonyl C₁₋₆ alkyl,
arylcarbonyl C₁₋₆ alkyl,
aryl C₁₋₆ alkylcarbonyl,
aryl C₁₋₆ alkylcarbonyl C₁₋₆ alkyl,
C₁₋₆ alkylthiocarbonylamino,
10 C₁₋₆ alkylthiocarbonylamino C₁₋₆ alkyl,
arylthiocarbonylamino C₁₋₆ alkyl,
aryl C₁₋₆ alkylthiocarbonylamino,
aryl C₁₋₆ alkylthiocarbonylamino C₁₋₆ alkyl,
C₁₋₈ alkylaminocarbonyl C₁₋₆ alkyl,
15 arylaminocarbonyl C₁₋₆ alkyl,
aryl C₁₋₈ alkylaminocarbonyl, or
aryl C₁₋₈ alkylaminocarbonyl C₁₋₆ alkyl,
wherein the alkyl or N atoms may be unsubstituted or
substituted with one or more substituents selected from R²¹ and
20 R²²; or R⁸ and R⁹ are combined to form oxo;
- R¹⁰ and R¹¹ are each independently selected from
hydrogen,
aryl,
25 halogen,
aryl-(CH₂)_p-,
hydroxyl,
C₁₋₈ alkylcarbonylamino,
aryl C₁₋₅ alkoxy,
C₁₋₅ alkoxycarbonyl,
30 aminocarbonyl,
C₁₋₈ alkylaminocarbonyl,
C₁₋₆ alkylcarbonyloxy,
C₃₋₈ cycloalkyl,
amino,

- C₁₋₆ alkylamino,
 amino C₁₋₆ alkyl,
 arylaminocarbonyl,
 aryl C₁₋₅ alkylaminocarbonyl,
 5 aminocarbonyl,
 aminocarbonyl C₁₋₆ alkyl,
 hydroxycarbonyl,
 hydroxycarbonyl C₁₋₆ alkyl,
 C₁₋₈ alkyl, either unsubstituted or substituted, with one or more
 10 groups selected from: halogen, hydroxyl,
 C₁₋₅ alkylcarbonylamino, aryl C₁₋₅ alkoxy,
 C₁₋₅ alkoxycarbonyl, aminocarbonyl, C₁₋₅ alkylamino-
 carbonyl, C₁₋₅ alkylcarbonyloxy, C₃₋₈ cycloalkyl, oxo,
 amino, C₁₋₃ alkylamino, amino C₁₋₃ alkyl, arylamino-
 15 carbonyl, aryl C₁₋₅ alkylaminocarbonyl, aminocarbonyl,
 aminocarbonyl C₁₋₄ alkyl, hydroxycarbonyl, or
 hydroxycarbonyl C₁₋₅ alkyl,
 HC≡C(CH₂)_r -
 C₁₋₆ alkyl-C≡C(CH₂)_r -,
 20 C₃₋₇ cycloalkyl-C≡C(CH₂)_r -,
 aryl-C≡C(CH₂)_r -,
 C₁₋₆ alkylaryl-C≡C(CH₂)_r -,
 H₂C=CH(CH₂)_r -,
 C₁₋₆ alkyl-CH=CH(CH₂)_r -,
 25 C₃₋₇ cycloalkyl-CH=CH(CH₂)_r -,
 aryl-CH=CH(CH₂)_r -,
 C₁₋₆ alkylaryl-CH=CH(CH₂)_r -,
 C₁₋₆ alkyl-SO₂(CH₂)_r -,
 C₁₋₆ alkylaryl-SO₂(CH₂)_r -,
 30 C₁₋₆ alkoxy,
 aryl C₁₋₆ alkoxy,
 aryl C₁₋₆ alkyl,
 C₁₋₆ alkylamino C₁₋₆ alkyl,
 arylamino,

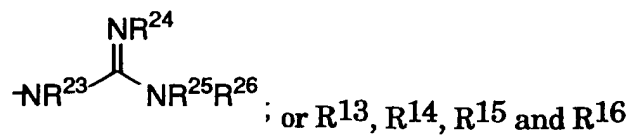
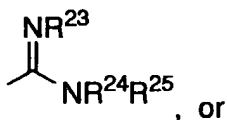
- arylamino C₁₋₆ alkyl,
aryl C₁₋₆ alkylamino,
aryl C₁₋₆ alkylamino C₁₋₆ alkyl,
arylcarbonyloxy,
5 aryl C₁₋₆ alkylcarbonyloxy,
C₁₋₆ dialkylamino,
C₁₋₆ dialkylamino C₁₋₆ alkyl,
C₁₋₆ alkylaminocarbonyloxy,
C₁₋₈ alkylsulfonylamino,
10 C₁₋₈ alkylsulfonylamino C₁₋₆ alkyl,
arylsulfonylamino C₁₋₆ alkyl,
aryl C₁₋₆ alkylsulfonylamino,
aryl C₁₋₆ alkylsulfonylamino C₁₋₆ alkyl,
C₁₋₈ alkoxycarbonylamino,
15 C₁₋₈ alkoxycarbonylamino C₁₋₈ alkyl,
aryloxycarbonylamino C₁₋₈ alkyl,
aryl C₁₋₈ alkoxycarbonylamino,
aryl C₁₋₈ alkoxycarbonylamino C₁₋₈ alkyl,
C₁₋₈ alkylcarbonylamino,
20 C₁₋₈ alkylcarbonylamino C₁₋₆ alkyl,
arylcarbonylamino C₁₋₆ alkyl,
aryl C₁₋₆ alkylcarbonylamino,
aryl C₁₋₆ alkylcarbonylamino C₁₋₆ alkyl,
aminocarbonylamino C₁₋₆ alkyl,
25 C₁₋₈ alkylaminocarbonylamino,
C₁₋₈ alkylaminocarbonylamino C₁₋₆ alkyl,
arylaminocarbonylamino C₁₋₆ alkyl,
aryl C₁₋₈ alkylaminocarbonylamino,
aryl C₁₋₈ alkylaminocarbonylamino C₁₋₆ alkyl,
30 aminosulfonylamino C₁₋₆ alkyl,
C₁₋₈ alkylaminosulfonylamino,
C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
arylaminosulfonylamino C₁₋₆ alkyl,
aryl C₁₋₈ alkylaminosulfonylamino,

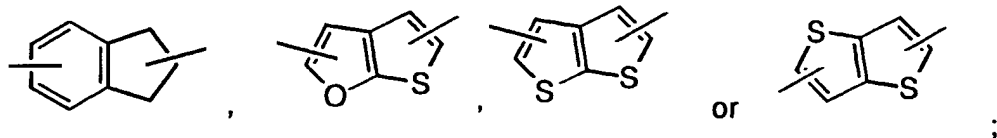
- aryl C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
 C₁₋₆ alkylsulfonyl,
 C₁₋₆ alkylsulfonyl C₁₋₆ alkyl,
 arylsulfonyl C₁₋₆ alkyl,
 5 aryl C₁₋₆ alkylsulfonyl,
 aryl C₁₋₆ alkylsulfonyl C₁₋₆ alkyl,
 C₁₋₆ alkylcarbonyl,
 C₁₋₆ alkylcarbonyl C₁₋₆ alkyl,
 arylcarbonyl C₁₋₆ alkyl,
 10 aryl C₁₋₆ alkylcarbonyl,
 aryl C₁₋₆ alkylcarbonyl C₁₋₆ alkyl,
 C₁₋₆ alkylthiocarbonylamino,
 C₁₋₆ alkylthiocarbonylamino C₁₋₆ alkyl,
 arylthiocarbonylamino C₁₋₆ alkyl,
 15 aryl C₁₋₆ alkylthiocarbonylamino,
 aryl C₁₋₆ alkylthiocarbonylamino C₁₋₆ alkyl,
 C₁₋₈ alkylaminocarbonyl C₁₋₆ alkyl,
 arylaminocarbonyl C₁₋₆ alkyl,
 aryl C₁₋₈ alkylaminocarbonyl,
 20 aryl C₁₋₈ alkylaminocarbonyl C₁₋₆ alkyl,
 C₇₋₂₀ polycyclyl C₀₋₈ alkylsulfonylamino C₀₋₆ alkyl,
 C₇₋₂₀ polycyclyl C₀₋₈ alkylcarbonylamino C₀₋₆ alkyl,
 C₇₋₂₀ polycyclyl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 C₇₋₂₀ polycyclyl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl, or
 25 C₇₋₂₀ polycyclyl C₀₋₈ alkyloxycarbonylamino C₀₋₆ alkyl
 wherein the alkyl or N atoms may be unsubstituted or
 substituted with one or more substituents selected from R²¹ and
 R²², wherein the polycyclyl may be unsubstituted or substituted
 with R³¹, R³², R³³ and R³⁴, and provided that the carbon atom to
 30 which R¹⁰ and R¹¹ are attached is itself attached to no more than
 one heteroatom; or R¹⁰ and R¹¹ are combined to form oxo;

R¹² is selected from
 hydroxy,

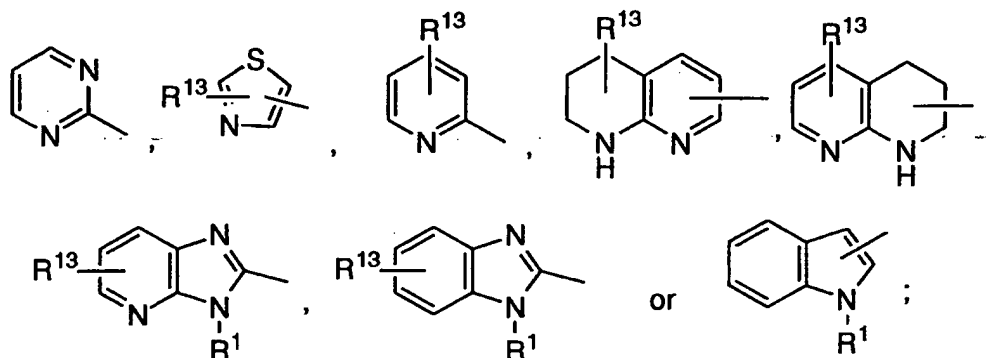
C₁₋₈ alkyloxy,
 aryl C₀₋₆ alkyloxy,
 C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
 aryl C₀₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
 5 C₁₋₆ dialkylaminocarbonylmethyloxy,
 aryl C₁₋₆ dialkylaminocarbonylmethyloxy or
 an L- or D-amino acid joined by an amide linkage and
 wherein the carboxylic acid moiety of said amino acid
 is as the free acid or is esterified by C₁₋₆ alkyl; and

10 R¹³, R¹⁴, R¹⁵ and R¹⁶ are each independently selected from
 hydrogen,
 C₁₋₁₀ alkyl,
 aryl C₀₋₈ alkyl,
 15 thio,
 amino C₀₋₈ alkyl,
 C₁₋₃ acylamino C₀₋₈ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 20 aryl C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₁₋₄ alkoxyamino C₀₋₈ alkyl,
 hydroxy C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyl,
 25 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyloxy,
 hydroxy C₁₋₆ alkylamino C₀₋₆ alkyl,
 hydroxy C₀₋₆ alkyl,





then X is selected from



and the pharmaceutically acceptable salts thereof.

5

2. The compound of Claim 1, wherein

Y is selected from

- C0-8 alkylene,
- 10 C3-10 cycloalkyl,
- C0-8 alkylene-NR⁵-CO-C0-8 alkylene,
- C0-8 alkylene-CONR⁵-C0-8 alkylene,
- C0-8 alkylene-O-C0-8 alkylene,
- C0-8 alkylene-NR⁵-C0-8 alkylene,
- 15 C0-8 alkylene-S(O)₀₋₂-C0-8 alkylene,
- C0-8 alkylene-SO₂-NR⁵-C0-8 alkylene,
- C0-8 alkylene-NR⁵-SO₂-C0-8 alkylene,
- C0-8 alkylene-CO-C0-8 alkylene,
- (CH₂)₀₋₆ aryl(CH₂)₀₋₆,
- 20 (CH₂)₀₋₆ aryl-CO-(CH₂)₀₋₆,
- (CH₂)₀₋₆ aryl-CO-NH-(CH₂)₀₋₆, or
- $$\begin{array}{c} \text{OH} \\ | \\ (\text{CH}_2)_{0-8}\text{CH}(\text{CH}_2)_{0-8} \end{array};$$

Z is $(\text{CH}_2)_m$ where m is zero; and

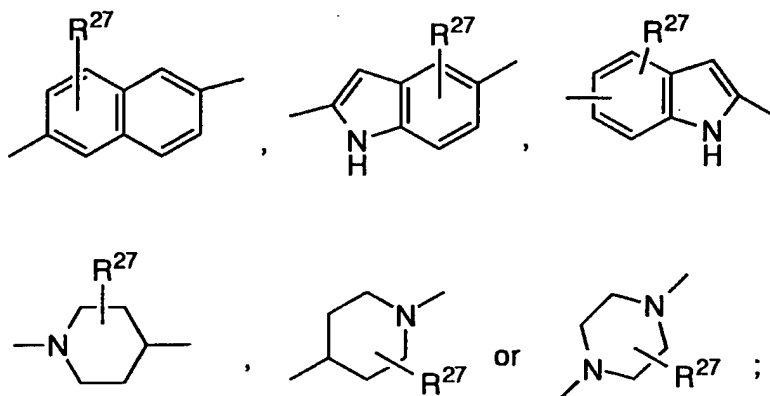
and the pharmaceutically acceptable salts thereof.

5

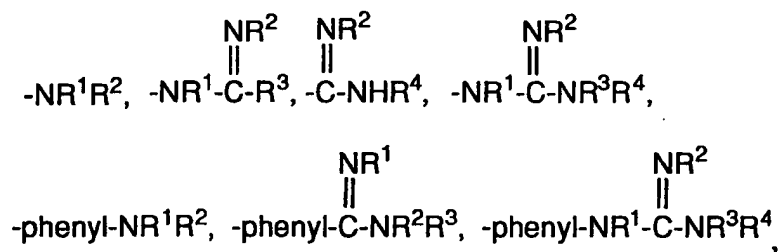
3. The compound of Claim 2, of the formula

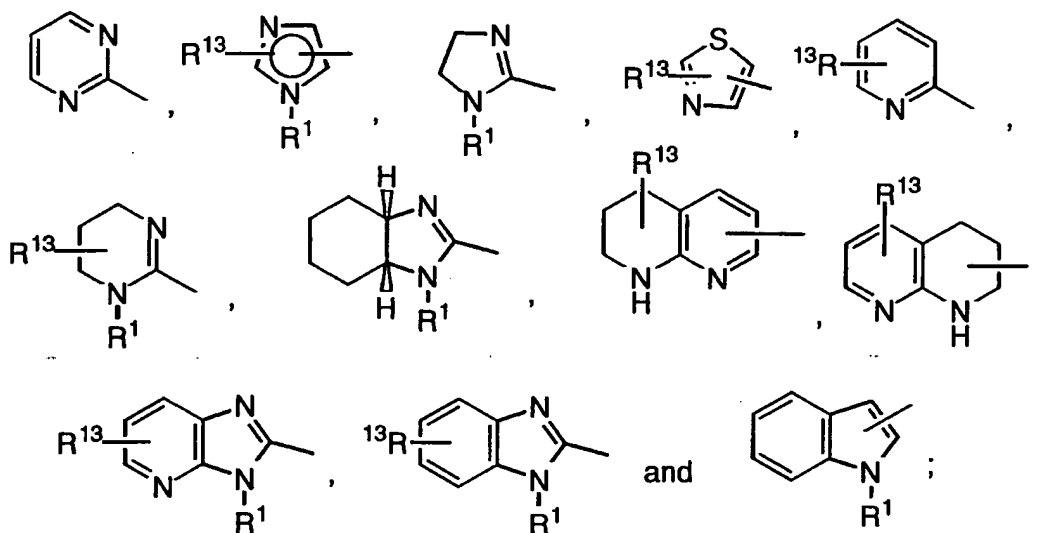
X-Y-Ring-A-B

10 wherein Ring is selected from



X is selected from

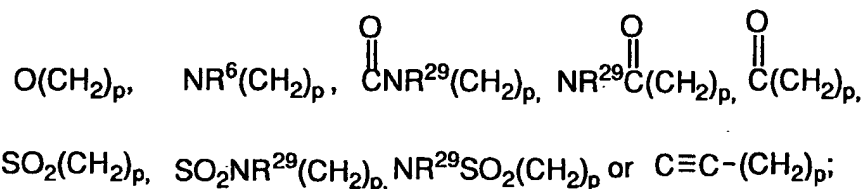




Y is selected from

- C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR⁵-CO-C₀₋₈ alkylene,
 C₀₋₈ alkylene-CONR⁵-C₀₋₈ alkylene,
 C₀₋₈ alkylene-O-C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR⁵-C₀₋₈ alkylene,
 C₀₋₈ alkylene-S(O)₀₋₂-C₀₋₈ alkylene,
 C₀₋₈ alkylene-SO₂-NR⁵-C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR⁵-SO₂-C₀₋₈ alkylene or
 (CH₂)₀₋₆ aryl(CH₂)₀₋₆;

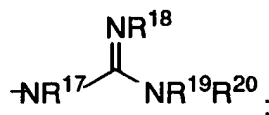
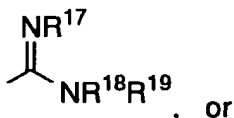
A is selected from



- 15 where p is an integer from 0 to 3;

R¹, R², R³, R⁴, R⁵, R⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²³, R²⁴, R²⁵, R²⁶, R²⁷ and R²⁹ are each independently selected from

- hydrogen,
 C₁₋₁₀ alkyl,
 aryl C₀₋₈ alkyl,
 amino C₀₋₈ alkyl,
 5 C₁₋₃ acylamino C₀₋₈ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyl,
 10 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyloxy,
 hydroxy C₀₋₆ alkyl,

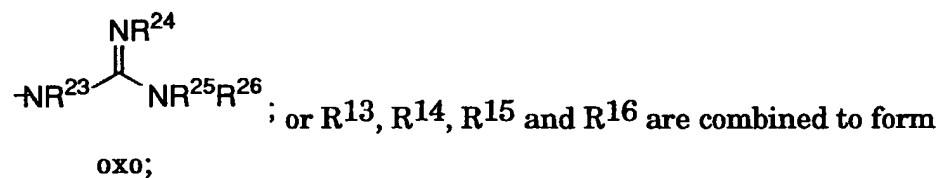
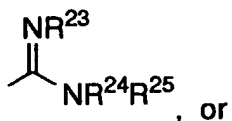


- 15 R¹⁰ and R¹¹ are each independently selected from
 hydrogen,
 fluorine,
 C₁₋₈ alkyl,
 hydroxyl,
 20 C₃₋₈ cycloalkyl,
 aryl C₀₋₆ alkyl,
 C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₀₋₆ dialkylamino C₀₋₆ alkyl,
 C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
 25 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
 C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
 aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
 C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,

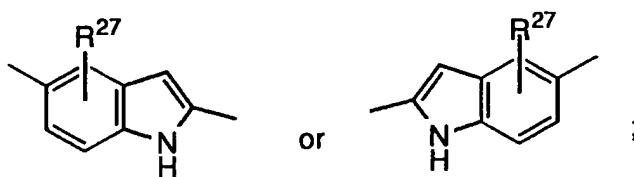
5 C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
C₁₋₆ alkylcarbonyl C₀₋₆ alkyl or
aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl;

10 R¹² is selected from
hydroxy,
C₁₋₈ alkyloxy,
aryl C₀₋₆ alkyloxy,
C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy or
aryl C₀₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy;

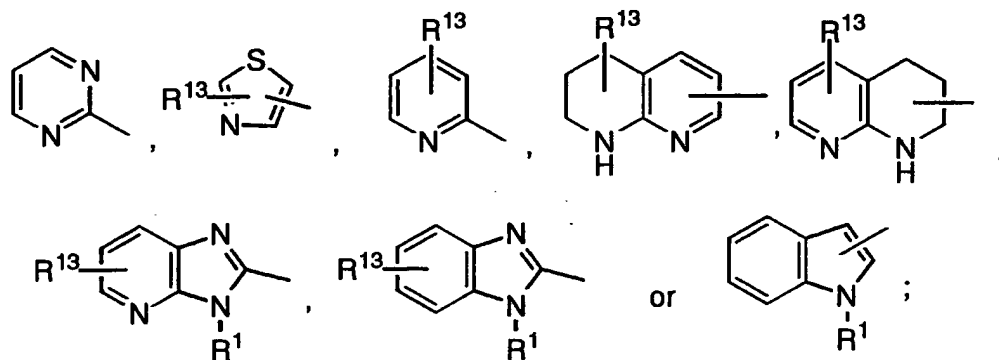
15 R¹³, R¹⁴, R¹⁵ and R¹⁶ are each independently selected from
hydrogen,
C₁₋₁₀ alkyl,
aryl C₀₋₈ alkyl,
20 amino C₀₋₈ alkyl,
C₁₋₃ acylamino C₀₋₈ alkyl,
C₁₋₆ alkylamino C₀₋₈ alkyl,
C₁₋₆ dialkylamino C₀₋₈ alkyl,
C₁₋₄ alkoxy C₀₋₆ alkyl,
25 carboxy C₀₋₆ alkyl,
C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
carboxy C₀₋₆ alkyloxy,
hydroxy C₀₋₆ alkyl,



provided that when Ring is

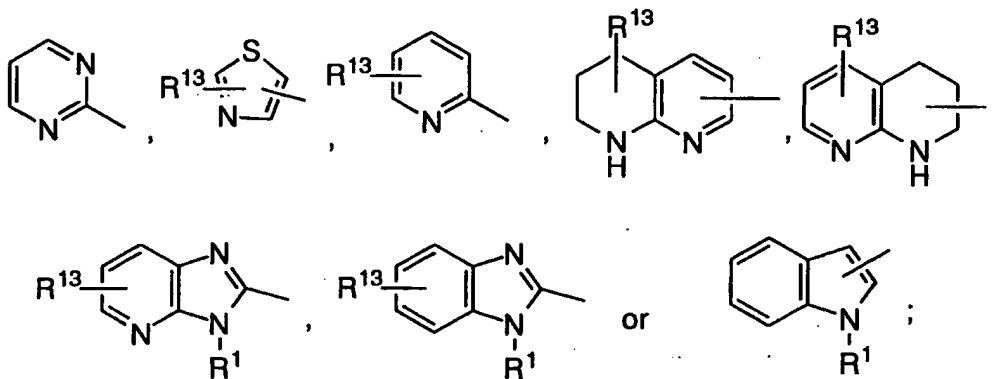


5 then X is selected from



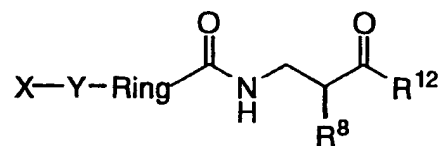
and the pharmaceutically acceptable salts thereof.

4. The compound of Claim 3, wherein X is selected from



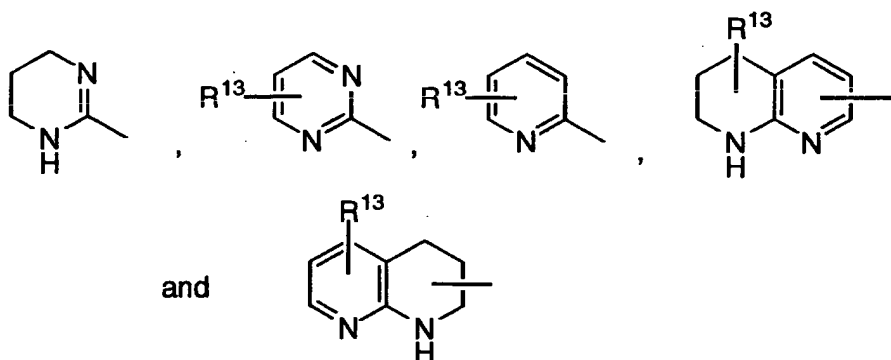
and the pharmaceutically acceptable salts thereof.

5. The compound of Claim 4, of the formula



5

X is selected from



Y is selected from

C0-8 alkylene,

10 C0-8 alkylene-NR⁵-C0-8 alkylene; and

R¹² is selected from

hydroxy or

C1-8 alkyloxy;

and the pharmaceutically acceptable salts thereof .

6. The compound of Claim 5, selected from

- 5 [6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino- β -alanine ethyl ester;
- [6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino- β -alanine;
- 10 6-[(N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl]carbonyl-2(S)-phenylsulfonylamino- β -alanine ethyl ester;
- 6-[(N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino- β -alanine;
- 15 4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester;
- 20 4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino- β -alanine;
- 6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl- β -alanine ethyl ester;
- 25 6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl- β -alanine; or
- 30 6-[(1,4,5,6-Tetrahydropyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonylamino- β -alanine;

and the pharmaceutically acceptable salts thereof.

7. The compound of Claim 6, selected from

35

[6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino- β -alanine;

5 6-([N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl)carbonyl-2(S)-phenylsulfonylamino- β -alanine;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino- β -alanine; or

10 6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl- β -alanine;

and the pharmaceutically acceptable salts thereof.

15 8. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition made by combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

20 10. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

25 11. A method of eliciting a vitronectin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

30 12. The method of Claim 11, wherein the vitronectin antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of angiogenesis, inhibition of diabetic retinopathy, inhibition of macular degeneration or inhibition of tumor growth.

13. The method of Claim 12, wherein the vitronectin antagonizing effect is the inhibition of bone resorption.

5 14. A method of treating or preventing a condition mediated by antagonism of a vitronectin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

10 15. The method of Claim 14, wherein the condition is selected from the group consisting of osteoporosis and cancer.

16. The method of Claim 15, wherein the condition is osteoporosis.

15 17. A method of inhibiting bone resorption in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

20 18. A method of treating osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

25 19. A method of preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

30 20. A method of eliciting a vitronectin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

21. A method of treating or preventing a condition mediated by antagonism of a vitronectin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

5

22. A method of inhibiting bone resorption in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

10

23. A method of treating osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

15

24. A method of preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

20

25. The use of the compound of Claim 1 in the preparation of a medicament for the treatment or prevention of a condition selected from: osteoporosis, bone resorption, tumor growth, cancer, restenosis, arteriosclerosis, diabetic retinopathy, macular degeneration or angiogenesis in a mammal in need thereof.

25

26. A drug which is useful for treating or preventing a condition selected from: osteoporosis, bone resorption, tumor growth, cancer, restenosis, arteriosclerosis, diabetic retinopathy, macular degeneration or angiogenesis in a mammal in need thereof, the effective ingredient of the said drug being the compound of Claim 1.

30

27. A method of treating tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 and one or more agents known to be cytotoxic or antiproliferative.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19349

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/32710 A1 (MERCK & CO., INC.) 07 December 1995, claims 1-25.	1-27
A	US 5,416,099 A (HARTMAN et al.) 16 May 1995, claims 1-6.	1-27
A	XUE, C-B. et al. Design, synthesis and in vitro activities of a series of benzimidazole/benzoxazole glycoprotein IIb/IIIa inhibitors. Biorg. & Medic. Chem. Lett. 1996, Volume 6, No. 3, pages 339-344, especially tables 1 and 2 on pages 342 and 343.	1-27



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
A document defining the general state of the art which is not considered to be of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
E earlier document published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O document referring to an oral disclosure, use, exhibition or other means	*A* document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

20 JANUARY 1998

Date of mailing of the international search report

23 FEB 1998

Name and mailing address of the ISA/US
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Authorized officer

CHANA AULAKH

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19349

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19349

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/18, 31/19, 31/44, 31/47, 31/195, 31/405, 31/415, 31/425, 31/435, 31/505; C07C 63/00, 307/06, 307/08, 307/10; C07D 209/40, 213/89, 217/08, 233/44, 233/88, 239/08, 239/14, 239/42

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/275, 300, 303, 310, 352, 357, 365, 371, 396, 398, 415, 563, 603, 613, 616; 544/323, 332; 546/118, 122, 143, 290, 291, 301, 304, 309, 310, 311, 312; 548/195, 300.1, 308.4, 335.5, 495; 560/34; 564/86, 147

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/275, 300, 303, 310, 352, 357, 365, 371, 396, 398, 415, 563, 603, 613, 616; 544/323, 332; 546/118, 122, 143, 290, 291, 301, 304, 309, 310, 311, 312; 548/195, 300.1, 308.4, 335.5, 495; 560/34; 564/86, 147

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. The species are as follows:

I. Compounds of formula of claim 1 where Ring or X is 6-membered hetero ring containing O, S and N as the heteroatoms, classifiable in class 544, subclass 2+.

II. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing O and N as the heteroatoms, classifiable in class 544, subclass 63+.

III. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing four N as the heteroatoms, classifiable in class 544, subclass 179.

IV. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing three N as the heteroatoms, classifiable in class 544, subclass 180.

V. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing two N as the heteroatoms, classifiable in class 544, subclass 224+.

VI. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing only one N as the heteroatom, classifiable in class 546, subclass 26+.

VII. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing O, S and N as the heteroatoms, classifiable in class 548, subclass 122+.

VIII. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing four N as the heteroatoms, classifiable in class 548, subclass 250+.

IX. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing three N as the heteroatoms, classifiable in class 548, subclass 255+.

X. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing two N as the heteroatoms, classifiable in class 548, subclass 300.1+.

XI. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing only one N as the heteroatom, classifiable in class 548, subclass 400+.

XII. Compounds of formula of claim 1 where Ring or X is a hetero ring containing only S as the heteroatoms, classifiable in class 549, subclass 1+.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19349

XIII. Compounds of formula of claim 1 where Ring or X is a hetero ring containing only O as the heteroatoms, classifiable in class 549, subclass 200+.

XIV. Compounds of formula of claim 1 containing carboxylic acid ester and either Ring or X is not a hetero ring, classifiable in class 560, subclass 11+.

XV. Compounds of formula of claim 1 containing amino nitrogen and either Ring or X is not a hetero ring, classifiable in class 564, subclass 1+.

The claims are deemed to correspond to the species listed above in the following manner:

Species V and VI. Claims 6 and 7.

The following claims are generic: Claims 1-5 and 8-27.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

There is no common core Which in the Markush Practice, is a significant structural element shared by all the alternatives; see PCT Administrative Instructions Annex B Part I (f) (i) (B) (1) and further, all alternatives do not belong to a recognized class of chemical compounds in the art to which the invention pertains; see supra (B) (2).